Anti-aggressive effects of alnespirone (S20499), a potent 5-HT1A receptor agonist, in wild-type rats

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control. There were no significant differences between baseline levels in 5-HT and DA in fluvoxamine treated group and those in saline control following chronic administration of fluvoxamine 10 mg/kg/day for 14 days using osmotic minipump. Additional i.p. injection of fluvoxamine 30 mg/kg, 60 mg/kg after chronic pretreatment with fluvoxamine showed significant and dose-dependent increase in 5-HT compared to saline pretreated animals. This increase in 5-HT was more continuous compared to the changes in 5-HT in single administration of fluvoxamine.

These results suggest that chronic administration of fluvoxamine and other SSRIs show prolonged elevation in extracellular levels of 5-HT and down regulation of 5HT1A autoreceptor may be involved in these net increase in serotonergic neurotransmission.

P-5-2 Multiple 5-HT Receptor Subtypes Regulate [^{3}H]5-HT Release in Terminal Projection Areas: Superfusion Studies in Rat and Mice Brain

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In order to determine whether multiple 5-HT receptor subtypes might be involved in the regulation of 5-HT release by axon terminals, electrically-evoked release of [^{3}H]5-HT was examined in frontal cortex and hippocampus slices obtained from wild-type and 5-HT_{1B} knock-out mice, as well as in rat hippocampal slices. As expected, the selective 5-HT_{1B} agonist CP-93129 (100 nM) inhibited evoked [^{3}H]5-HT release in hippocampal and cortical preloaded slices from wild-type mice but not from 5-HT_{1B} knock-out mice. However, the non-selective 5-HT agonist 5-carboxyamidotryptamine (5-CT; 100 nM) inhibited evoked [^{3}H]5-HT release in hippocampal slices and in cortical slices obtained from both controls and mutants. In rat hippocampus slices, the 5-$HT_{1B/1D/1F}$ agonist sumatriptan (1–1000 nM) and CP 93129 (1–300 nM) induced a dose-dependent inhibition of [^{3}H]5-HT release, which in both cases was significantly less than that induced by 5-CT (1–1000 nM). While the effects of CP 93129 and sumatriptan were both blocked by cyanopindolol (1 μM), only that of sumatriptan was blocked by the 5-$HT_{1D/2}$ antagonist mianserin (0.3 and 1 μM). On the other hand, the effect of CP 93129 was blocked by (−)propranolol (0.3 μM) which did not block that of sumatriptan. Furthermore, incubation of rat hippocampal slices with N-ethylmaleimide (NEM), a drug which inactivates $G_{i/o}$ proteins, abolished the effect of CP 93129 but not that of sumatriptan. These observations indicate that 5-HT release in the murine forebrain is regulated by more than one 5-HT receptor subtype.

P-5-3 Effect of a Combination of Befloxatone and a 5HT_{1A} Receptor Antagonist on Rat Cortical Serotonin Release

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Recent clinical studies have revealed a reduction in the onset of action and an enhanced antidepressant efficacy when selective serotonin reuptake inhibitors and MAOI are combined with (−)-pindolol, a 5-HT_{1A} receptor antagonist (Artigas et al, 1994, Arch. Gen. Psychiatry, 51, 248, Blier and Bergeron, 1995, J. Clin. Psychopharmacol., 15, 217). It has been proposed that this effect is due to the selective blockade by pindolol of somatic 5HT_{1A} autoreceptors involved in the negative feedback control of serotonergic neuron activity which relieves the inhibition of these neurons. In the present study, we have investigated the effects of a combination of befloxatone, a selective and reversible MAO-A inhibitor and SL88.0338-00, a selective and silent 5-HT_{1A} receptor antagonist, on extracellular levels (EC) of 5-HT in the frontal cortex and on the firing rate of dorsal raphe 5-HT neurons in the rat. In microdialysis experiments, acute administration of befloxatone (0.75 mg/kg, i.p.), did not modify the EC levels of 5-HT in frontal cortex of freely moving rats but decreased EC levels of DOPAC (−65%), HVA (−65%) and 5-HIAA (−25%). At this dose, befloxatone inhibited by 98% MAO-A activity and by 40% MAO-B in this brain region. SL88.0338-00 (2 mg/kg, i.p.) *per se* failed to modify the EC levels of 5-HT but its administration 20 min after befloxatone caused a 3 fold increase in EC levels of 5-HT. Acute administration of befloxatone decreased dorsal raphe firing activity (ED_{50} = 0.1 mg/kg, i.p.) and this effect was fully reversed by a subsequent injection of SL88.0338-00 (20 μg/kg, i.v). These results indicate that combination of a 5-HT_{1A} antagonist and a MAO-A inhibitor results in a marked enhancement of cortical 5-HT transmission.

P-5-4 Anti-Aggressive Effects of Alnespirone (S-20499), a Potent 5-HT_{1A} Receptor Agonist, in Wild-Type Rats

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Alnespirone (S-20499) is a novel amino chroman derivative (8[-4[N-(5-methoxychromane-3yl)N-propylaminobutyl]azaspiro[4,5]decane-7,9 dione) with potent and selective agonist properties at central serotonin (5-HT)$_{1A}$ receptors. Accordingly, since the 5-HT_{1A} receptor is known to play important roles in anxiety, alnespirone has reliably been reported to possess potent anxiolytic activity in a variety of animal behavioral models of anxiety. Besides the involvement in anxiety, 5-HT_{1A}-receptors are reported to be involved in aggressive behavior as well. Therefore, the present experiments investigated the effects of alnespirone on offensive and defensive aggression using a resident-intruder paradigm. Commencing at 30 min after subcutaneous (sc) injection of the drug (1, 5 and 10 mg/kg) or vehicle, the agonistic behavior of drugged resident male wild-type rats (offensive aggression test) or drugged intruder male wild-type rats (defensive aggression test) was examined by ethological procedures during a 10 min social encounter. Alnespirone exerted a potent dose-dependent decrease in offensive aggressive behavior in resident rats. This coincided with a compensatory increase in social explorative and social contact (mounting) behavior. Other non-social behavioral elements, i.e., exploration, grooming, inactivity, were not significantly affected by the drug treatment. In the defensive aggression test, alnespirone did not significantly change any behavioral element of the intruder rats. The data indicate that alnespirone effectively and specifically suppresses offensive aggression without interfering with adequate defensive aggressive behavior. Furthermore, these data provide evidence for the involvement of 5HT_{1A} receptors in the modulation of aggressive behavior.

P-5-5 Electrophysiological Effect of Alnespirone (S-20499) on the Rat Locus Coeruleus — Comparison with Buspirone

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Alnespirone (S-20499), a new chroman derivative, is a selective 5HT_{1A} receptor agonist which displays a slight affinity for α_1 and α_2 receptors (ratio $K_{0.5}$ 5HT_{1A}-α_1/α_2 = 330 and 240 for alnespirone and buspirone, respectively). Pharmacological studies have shown its anxiolytic and antidepressant activity in several animal models following single or repeated intraperitoneal, intramuscular, subcutaneous and oral administration. As other chemically related 5HT_{1A} agonists, such as buspirone, are also known to display *in vivo* α_2-adrenergic antagonist properties, we have tested the effects of alnespirone in comparison with buspirone on the inhibition of locus coeruleus (LC) noradrenergic neurons induced by the α_2-agonist clonidine. Histologically-confirmed extracellular recordings of LC spontaneous activity were performed on chloral hydrate-anesthetized rats with glass micropipettes. Clonidine (40 μg/kg i.p.) induced a rapid and complete inhibition of LC activity that was totally reversed by subsequent buspirone (10 mg/kg i.p.), unlike alnespirone (10 mg/kg i.p.) which did not affect the typical and slow recovery to baseline activity. On the other hand, although both compounds increased LC firing, clonidine-induced inhibition was blocked by prealable administration of buspirone but not alnespirone. These findings indicate that, *in vivo*, alnespirone, unlike buspirone, is devoid of significant α_2-adrenergic antagonist properties. The effect of buspirone may be due to its main metabolite (1-PP) which is not a metabolite of alnespirone.